

## REMARKS

Applicants respectfully request reconsideration and allowance of all pending claims.

### I. Status of the Claims

In this Amendment D, claims 1, 12, 13, 17, 50 and 52 have been amended to more particularly claim certain embodiments of the present disclosure. Specifically, claim 1 has been amended by: limiting X to NR<sub>4</sub>, by including hydrogen within the Markush group defining R<sub>2</sub>; removing hydrogen, alkyl and aryl from the Markush group define R<sub>4</sub> and adding biomolecule to the Markush group defining R<sub>6</sub>. Applicants submit that support for R<sub>4</sub> being a (CH<sub>2</sub>)<sub>n</sub>CO-biomolecule is apparent to one of ordinary skill in the art from a reading of the specification, particularly in context with the structure of Figure 1 and structure 13 of, for example, Figure 4. Applicants submit that it would be clear to one of ordinary skill in the art that a common means for attachment of a biomolecule containing an amino moiety would be via an acid moiety of the chelating agent, thereby resulting in an amide bond. This option is particularly illustrated and supported by the compound of structure 13 (see, e.g., Figure 4). Support for the addition of a biomolecule to the R<sub>6</sub> Markush group may be found in claim 1 as pending prior to the amendment made in Applicants' response dated September 2, 2008. The specification also supports the addition of biomolecule (see, for example, page 5, lines 27-28 and Figure 1). The specification at page 2, lines 1-20 and original claim 1 support inclusion of hydrogen within the R<sub>2</sub> Markush group and also support limiting the X Markush group to NR<sub>4</sub>.

Amendments to dependent claims 12, 13, 17 and 50 are made to conform the claims to the requirements of claim 1, and find support therein. Finally, the amendment to dependent claim 52 was made to conform the claim to the requirements of claim 38, and find support therein.

In addition to the above-noted amendments, Applicants have cancelled claims 9-10, 14-16, 24, and 26. Applicants previously cancelled claims 18-23, 27-35, 37 and 39-40. Accordingly, upon entry of this Amendment D, claims 1-8, 11-13, 17, 25, 36, 38 and 41-52 remain pending. Applicants previously withdrew from consideration at this time claims 4, 5, 8, 11, 13, 17 and 25, as being drawn to a non-elected species. Claims 1-3, 6, 7, 12, 36, 38 and 41-52 are therefore under consideration and examination at this time.

Applicants respectfully reserve the right to pursue the subject matter of one or more cancelled claims in a continuation or divisional application during the pendency of the present application.

### II. Allowed and Allowable Subject Matter

Applicants acknowledge allowance of claims 36, 38, 43-49 and 51.

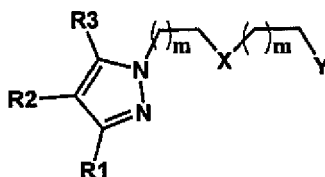
### III. Rejection under 35 U.S.C. §112, Second Paragraph

Claim 52 was rejected under 35 U.S.C. §112, second paragraph as indefinite. Claim 52 has been amended to change the phrase " $R_1 = R_3 = \text{CH}_3$ " to " $R_1$  or  $R_3 = \text{CH}_3$ " (emphasis added). When read in combination with claim 38, from which claim 52 depends, it is clear that claim 52 is directed, in relevant part, to an embodiment wherein  $R_1$  is  $\text{CH}_3$  and  $R_3$  is aryl, or vice versa. Accordingly, there is no contradiction in the limitations of these claims. Applicants therefore request reconsideration of the present rejection.

### IV. Rejection under 35 U.S.C. §103(a)

The Office has rejected claims 1-3, 6, 7, 12, 41, 42 and 50 under 35 U.S.C. §103(a) as obvious over "Coordination Capabilities of Pyrazolyl Containing Ligands Towards the *fac*-[Re(CO)<sub>3</sub>]<sup>+</sup> Moiety," by Alves et al. ("Alves et al. (2002)") in view of U.S. Pat. No. 5,066,479 to Hawthorne. Applicants submit that the rejected claims are patentable over the cited combination of references for the reasons set forth below.

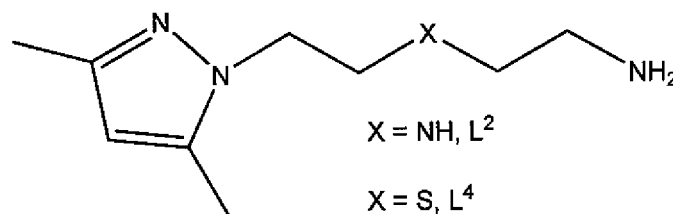
Independent claim 1, from which claims 2, 3, 6, 7, 12, 41, 42 and 50 depend, is directed to a chelating agent of the general formula:



M is 0 or 1 and X is  $\text{NR}_4$ . Y is  $\text{SR}_5$ ,  $\text{NHR}_5$  or  $\text{P}(\text{R}_5)_2$ , and  $R_1$  and  $R_3$  are the same or different and are selected from H, alkyl or aryl.  $R_2$  is H,  $\text{COOH}$ ,  $\text{NHR}_6$  or  $(\text{CH}_2)_n\text{COOR}_6$ .  $R_4$  is  $(\text{CH}_2)_n\text{CO-biomolecule}$ ,  $(\text{CH}_2)_n\text{COOR}_6$  or  $(\text{CH}_2)_n\text{OR}_6$ .  $R_5$  is H, alkyl, aryl,  $(\text{CH}_2)_n\text{COOR}_6$  or  $(\text{CH}_2)_n\text{OR}_6$ .  $R_6$  is H, a biomolecule, alkyl or aryl, and n is 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10.

Accordingly, it is to be noted that, in the structure of Applicants' claim 1, X is directed to a nitrogen-containing moiety,  $\text{NR}_4$ . Furthermore, the substituent on the nitrogen atom,  $R_4$ , is not H; rather,  $R_4$  is defined by the Markush group of  $(\text{CH}_2)_n\text{CO-biomolecule}$ ,  $(\text{CH}_2)_n\text{COOR}_6$  or  $(\text{CH}_2)_n\text{OR}_6$ . The compounds of independent claim 1 thus call for a tertiary amine as the X group. The tertiary amine may contain a group that allows ready derivatization with biomolecules or, alternatively, may already be derivatized with a biomolecule. Advantageously, such compounds retain the chelating properties (e.g., high specific activity, stability *in vitro* and *in vivo*) of the non-derivatized secondary amine, even after conjugation of the acid-bearing derivative with a biomolecule. (See, for example, the article by Alves et al., *Bioconjugate Chem.*, 2005, 16, 438, which is enclosed as Exhibit A here. In particular, see ligands L6 and L7; conjugated ligands L8 and L9; results discussed on pages 444-445, as well as the "Conclusion" on page 448. ("Alves et al. (2005)").

Alves et al. (2002) is directed to utilization of pyrazolyl-containing ligands for coordinating metal-carbonyl compounds. Among the coordinating compounds disclosed by Alves et al. are those designated L<sup>2</sup> and L<sup>4</sup>, the structures of which are shown below.



Alves et al. (2002) therefore disclose compounds that are limited to either a sulfur atom or a secondary amine at the X position. Stated another way, Alves et al. (2002) **fail to disclose or suggest a compound wherein X is a tertiary amine**. As such, they also fail to disclose or suggest that such compounds might be highly useful as a bifunctional chelating agent.

The deficiencies of Alves et al. (2002) are not overcome by the addition of Hawthorne. Specifically, Hawthorne also **fails to disclose or suggest** the compounds of independent claim 1, because the compounds disclosed by Hawthorne do not include a readily derivatizable tertiary amine substituent thereon. In fact, the substituent on "Y" (i.e., the pyrazolyl ring) that coordinates the metal atom "X" **does not even contain** a nitrogen atom; rather, it is an alkylborane substituent.

In view of the foregoing, it is to be noted that cited combination of references **fails to disclose or suggest each and every element** of claim 1. Furthermore, Applicants submit that there is simply **no motivation** to modify the disclosure of the cited references, because both are completely silent as to the ability of a tertiary amine to retain the chelating properties of the non-derivatized secondary amine analog compound. As a result, the Office has failed to establish a *prima facie* case of obvious. Reconsideration and withdrawal of the rejection of claim 1 is therefore requested.

Inasmuch as claims 2, 3, 6, 7, 12, 41, 42 and 50 depend from claim 1, these claims are submitted as patentable over the cited combination of references for at least the same reasons as those set forth with respect to claim 1. Reconsideration and withdrawal of the rejection of these claims is therefore requested, as well.

#### V. Request for Rejoinder

Applicants reiterate the rejoinder request from their previous submissions (including the response filed on September 2, 2008), in as much as the withdrawn claims are believed to be patentable over the cited combination of references, as well.

**CONCLUSION**

In view of the foregoing, Applicants request favorable reconsideration and allowance of all pending claims.

Applicants do not believe that a fee is due in connection with the submission of this Amendment D.

However, if the Office determines that a fee is due, authorization is hereby given to charge Deposit Account No. 13-1160.

Respectfully Submitted,

A handwritten signature in black ink, appearing to read "Anthony R. Kinney". The signature is fluid and cursive, with a large, stylized "A" and "K".

Anthony R. Kinney, Reg. No. 44,834  
Mallinckrodt Inc.  
675 McDonnell Boulevard  
Hazelwood, Missouri 63042  
(314) 654-8346